REMARKS

Claims 1-22 were previously cancelled without prejudice. Claims 29 and 36-38 are cancelled above without prejudice. Claim 29 is cancelled to avoid the Examiner's objection that the claim was directed to non-elected subject matter. As to the Examiner's objection to claims 32 on the same basis, Applicants point out that, due to the use of the conjunction "and" as opposed to "or", claim 32 is actually a species claim to the genus claim 30 on which claim 32 is dependent. As such, Applicants assert that claim 32 does not pertain to non-elected subject matter. Claims 36-38 are cancelled as redundant in view of the amendments to the corresponding independent claims. Applicants reserve the right to pursue any subject matter affected by the foregoing amendments/cancellation in co-pending or later filed continuation or divisional applications. Upon entry of the foregoing amendments, claims 23-28 and 30-35 will be before the Examiner for consideration.

Claims 23-38 are rejected under 35 USC § 112, first paragraph, as not meeting the written description requirement. Applicants assert that the amendments to claims 23 and 30 obviate this rejection. While claims 23, 30 and 34 have been amended to clarify that the rodent at issue is a rat or mouse, Applicants maintain that the specification reasonably supports use of the term rodent, and reserve the right to pursue rodent genus claims in related applications. Accordingly, in view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and withdrawal of this 35 USC § 112 written description rejection.

Claims 23-38 are rejected under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey possession of the invention. Applicants note that independent claims 23, 30, and 34 have been amended to recite that the non-human animal at issue is a rat or mouse. Based on the teachings of the subject application, it is clear that the inventors were in possession of the methods recited in claims 23 and 30, and the composition of claim 34, as amended, to produce a neuropathology corresponding to a neurodegenerative disease. Accordingly, in view of the foregoing

amendments and remarks, Applicants respectfully request the reconsideration and withdrawal of this 35 USC § 112 written description rejection.

Claims 23-38 are rejected under 35 USC § 112, first paragraph, as not being enabled. Applicants assert that the amendments to independent claims 23, 30, and 34 obviate this rejection. These claims have been amended to recite that the animal species to which the methods of claims 23 and 30 pertain, and the composition of claim 34 pertain, is a rat or mouse. These amendments have been made in accordance with the guidance provided at pages 5-10 of the outstanding office action. Based on the rationale set forth by the Examiner at such pages, Applicants believe that the scope of all of the rejected claims, as affected by the amendments to claims 23, 30, and 34 are fully enabled. Accordingly, Applicants respectfully request the reconsideration and withdrawal of this 35 USC § 112 enablement rejection.

Claims 23-28 and 34-38 are rejected under 35 USC 112, second paragraph, as being indefinite. The office action states that the recitation of a broad term followed by a more narrow term in the same claim renders claims 23 and 34 indefinite. Applicants traverse. Applicants believe that it is common place to have a generic term in a claim, and then narrowing language that further defines and narrows the generic term. Such a situation arises not infrequently during prosecution when claims are narrowed in response to various rejections. This notwithstanding, claims 23 and 34 have been amended to avoid any indefiniteness possibly created by the purported generic term followed by a narrowing term. Reconsideration of the rejection on this basis is requested.

Claim 35 is said to be indefinite based on the designation of P301L as the aberrant form of tau. Applicants respectfully assert that the amendment to claim 35 obviates this rejection. The nomenclature “P301L” is standard in the field of Neurodegenerative diseases. It is shorthand for describing specific mis-sense mutations (where a mutation in a sequence of nucleotides in DNA changes the codon for the amino acids in the protein gene product). The 'P' refers to the amino acid proline, '301' refers to nucleotide number 301 from the 5-prime end of

the tau DNA coding sequence, and 'L' refers to leucine. 'P301L' is shorthand for 'a mutation at position 301 causing leucine to be incorporated in tau instead of proline'. The attached reference (van Slegtenhorst M, Lewis J, Hutton M. The molecular genetics of the tauopathies. Exp Gerontol. 2000 Jul;35(4):461-71) illustrates the routine use of this nomenclature in the scientific literature for describing a variety of specific known mutations, in this case in the tau gene. The van Slegtenhorst reference, and the references cited therein, clearly establish that the nomenclature "P301L" is well understood and commonly used in the literature. As such, Applicants assert that its use in claim 35 creates no indefiniteness issues. In view of the foregoing remarks, Applicants respectfully request the reconsideration and withdrawal of the rejection on this basis.

The rejection of claim 37 is moot in light of the cancellation of this claim.

All grounds for rejection or objection having been addressed and overcome herein, it is respectfully urged that this application is in condition for allowance. Should the Examiner be of the opinion that there remain valid grounds on which any of the claims as herein amended may be rejected, it is respectfully requested that the undersigned be accorded the courtesy of a telephonic interview to address and overcome any such remaining grounds for rejection.

Respectfully submitted,

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Review

The molecular genetics of the tauopathies

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Abstract

The identification of mutations in the tau gene in frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17) demonstrated that there is a direct link between tau dysfunction and neurodegeneration. At least 11 missense mutations and a three base pair deletion (ΔK280) have been identified in exons 9–13. Additionally, five splice site mutations have been found in intron 10. The different FTDP-17 mutations have multiple effects on the biology and function of tau. These varied pathogenic mechanisms likely explain the wide range of clinical and neuropathological features observed in different families with FTDP-17. In addition to the tau mutations, a common extended haplotype in the tau gene also appears to be a risk factor in the development of the apparently sporadic tauopathies progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). The mechanism by which this common variability in the tau gene influences the development of these neurodegenerative diseases is unclear; however, it further suggests a central role for tau in the pathogenesis of several neurodegenerative conditions including Alzheimer's disease (AD).

Keywords: Tauopathies; Alzheimer's disease; Neurodegenerative diseases

1. Introduction

Tau is a microtubule-associated protein (MAP) that forms insoluble intraneuronal aggregates in many neurodegenerative diseases including Alzheimer's disease (AD), Pick's disease (PiD), frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (Dickson, 1997). These tauopathies share hyperphosphorylated deposited tau protein in the brain, but they differ in the composition and morphology of filaments and regional brain distribution (Spillantini et al., 1998a).

In the normal brain, tau plays a major role in the dynamic behaviour and the stabilisation

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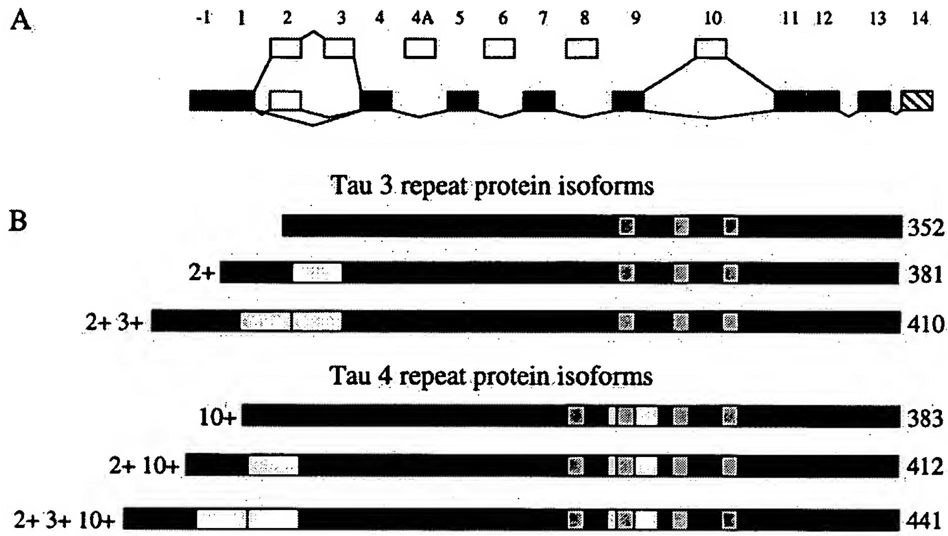

Fig. 1. *The tau gene and six protein isoforms in human brain.* A. Schematic representation of the tau gene. Alternatively spliced exons 2,3 and 10 are shown above the constitutive exons. Exons 4A, 6 and 8 are generally not spliced into human tau mRNA and most transcripts retain the intron between exons 13 and 14. B. The six Tau isoforms with alternatively spliced exons 2, 3 and 10, indicated by pink boxes. Exon 9–12 encode microtubule binding repeats (grey boxes). Alternative splicing of exon 10 gives rise to Tau isoforms with 4 (exon 10 +) or 3 (exon 10-) binding repeats.

of neuronal microtubules (MT) (LoPresti et al., 1995). Tau function is modulated by six major protein isoforms generated by alternative splicing. The heterogeneity of tau is also affected by post-translational modifications such as phosphorylation and glycation (Hutton, 1999).

The interaction between tau and tubulin is mediated by four MT binding repeats (31–32 amino acids) encoded by exons 9–12 (Lee et al., 1989). Alternative splicing of exon 10 gives rise to isoforms with 3 (exon 10 −) or 4 (exon 10 +) repeat domains (3R and 4R tau) at the C-terminus (Goedert et al., 1989) (Fig. 1). Tau exon 10 splicing is developmentally regulated so that only 3R tau is present in human foetal brain while the ratio of 3R to 4R isoforms is approximately 1:1 in adult brain. Different brain regions also differ in the relative levels of 3R and 4R isoforms with granule cells in the hippocampal formation reported to have only 3R tau (Goedert et al., 1989). Mouse brains differ from human brains by only expressing tau isoforms containing all four microtubule binding domains (Kosik et al., 1989).

2. Identification of tau mutations in FTDP-17

FTDP-17 is characterised by behavioural, cognitive and motor disturbances (Foster et al., 1997). Pathological changes in the brain include fronto-temporal atrophy with neuronal loss, grey and white matter gliosis and superficial cortical spongiform. In addition,

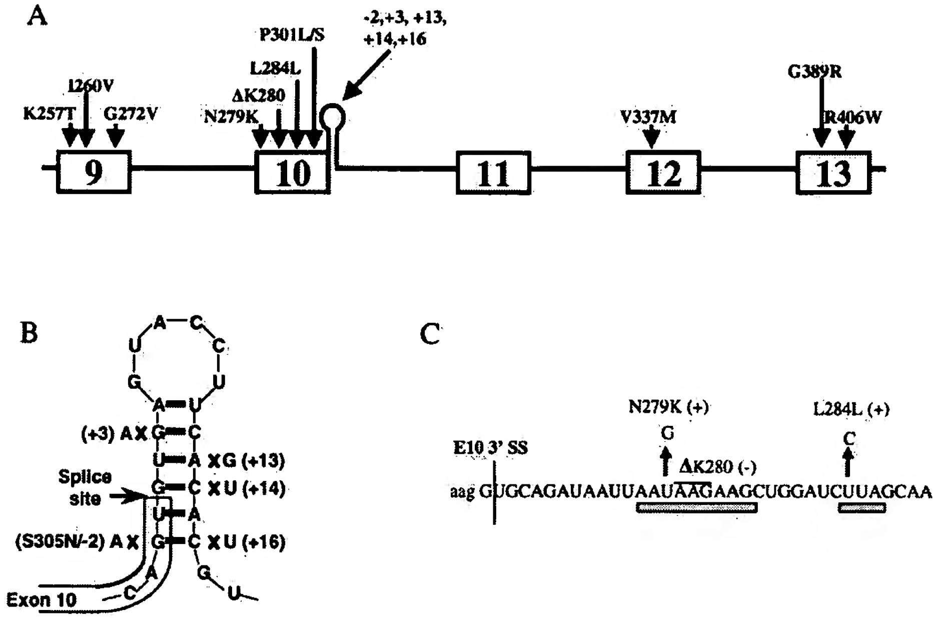

Fig. 2. *Mutations in the tau gene associated with FTDP-17.* A. Exons 9–13 of the tau gene are shown with mutations indicated. To date, all pathogenic mutations have been found in exons 9–13. Eleven missense mutations, a deletion mutation (ΔK280) and five mutations in the 5′ splice site of exon 10 have been identified. B. Mutations in the 5′ splice site of exon 10 are predicted to disrupt a stem-loop that regulates alternative splicing of exon 10. Disruption of the stem-loop is predicted to increase recognition of exon 10 by the U1 snRNP. C. The splicing mutations N279K and ΔK280 alter a poly-purine positive *cis*-element. The N279K mutation strengthens this element resulting in increased exon 10+ mRNA while the ΔK280 mutation abolishes the poly-purine tract and reduces exon 10+ mRNA. The L284L mutation eliminates a proposed negative regulatory element and causes increased incorporation of exon 10 into tau mRNA. (+) and (−) symbols beside each mutation indicates its effect on exon 10 splicing.

intraneuronal tau inclusions with the variable occurrence of glial inclusions are present in FTDP-17 brains (Dickson, 1997). The pattern of inheritance in FTDP-17 is autosomal dominant with an early age of onset (45–65 years).

The identification of mutations in tau associated with FTDP-17 (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998b) provided direct evidence that tau dysfunction can lead to neurodegeneration. To date, 11 missense mutations, a three base pair deletion (ΔK280) and five splice site mutations have been identified in over 50 FTDP-17 families (Fig. 2) (Hutton, 1999). All of the known mutations occur in the C-terminal end of tau, with the majority affecting exons 9–12, which encode the microtubule-binding repeats.

The variability in tau pathology observed in FTDP-17 can largely be explained by the type of mutation in tau (Table 1) (Hardy et al., 1998). Missense mutations outside exon 10 (G272V, V337M, R406W) lead to a predominantly neuronal pathology with straight filaments composed of all six isoforms. These filaments are similar to the paired helical filaments (PHFs) and straight filaments observed in AD. In contrast, missense (P301L, N279K) or splice site mutations that affect exon 10 result in both neuronal and glial tau

Table 1
Correlation between FTDP-17 mutations and tau pathology. (Only mutations with studied Tau neuropathology are presented (reviewed in Hutton, 1999) and from unpublished data (G389R and exon 10 + 13 mutations))

Mutation type	Mutations	Soluble tau	Tau inclusions	Tau filaments
Missense NOT Exon 10	G272V V337M G389R R406W	Normal ratio of 4 to 3 repeat	All six isoforms	AD-like PHF
Missense in exon 10	P301L P301S	Reduced 4 repeat in affected brain regions[a]	4 Repeat predominates	Variable, long periodicity
Exon 10 splice mutations	+3, +13, +14, +16[b] N279K[c]	Increased 4 repeat	4 Repeat predominates	Long periodicity

[a] P301L mutation causes the selective incorporation of 4R Tau into inclusions reducing the soluble 4R to 3R ratio however this effect is limited to brain regions affected in FTDP-17, unaffected regions have a normal ratio in soluble tau (Hong et al., 1998).

[b] Exon 10 5′ splice site intronic mutations numbered from 3′ end of exon 10.

[c] The N279K missense mutation alters exon 10 alternative splicing and is thus included with the splice mutations (Hong et al., 1998).

pathology, with filaments consisting predominantly of four repeat tau isoforms. The filaments in these cases are variable but have a different morphology (often including longer periodicity) than the PHFs that comprise the neurofibrillary tangles observed in AD.

3. Potential pathogenic mechanisms of tau mutations in FTDP-17

3.1. Missense mutations that disrupt tau-microtubule interactions and alter tau polymerisation into filaments

The missense mutations identified to date are either within or close to the microtubule-binding domains. In vitro studies have demonstrated that the majority of FTDP-17 missense mutations disrupt tau binding to the microtubules (Hasegawa et al., 1998; Hong et al., 1998; Dayanandan et al., 1999; Rizzu et al., 1999). Recombinant 4R tau binding to taxol stabilised microtubule dimers is reduced by most of the missense mutations (G272V, P301L, P301S, V337M, R406W) and by the ΔK280 deletion. In each case, the mutation affects both the affinity of tau (kDa) for microtubules and the binding capacity (β_{max}) (Hong et al., 1998). The majority of missense mutations also reduce the ability of tau to polymerise tubulin. The mutations increase the lag time, reduce the rate of polymerisation and reduce the total polymerised tubulin formed (Hasegawa et al., 1998; Hong et al., 1998; Rizzu et al., 1999). Studies in transfected Chinese Hamster Ovarian cells showed that the P301L, V337M and R406W missense mutations were able to reduce the ability to form microtubule-filled processes after cytochalasin B treatment (Dayanandan et al., 1999). In summary, cell-free as well as transfected cell studies have

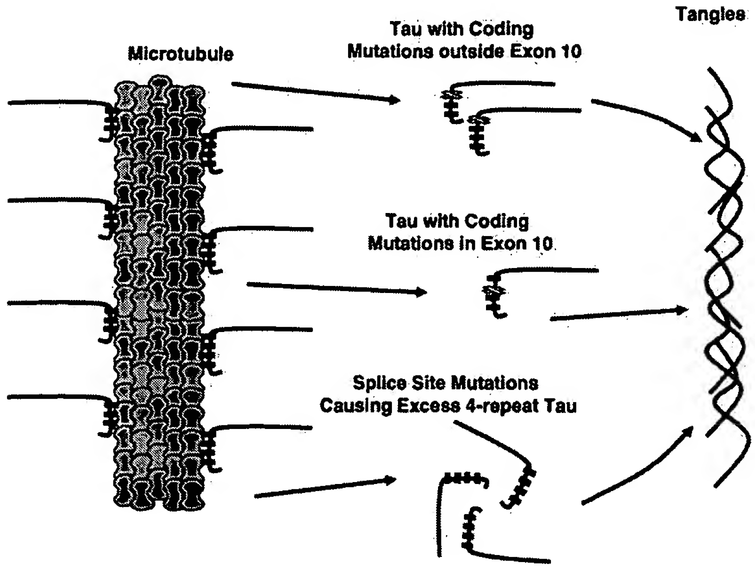

Fig. 3. *Proposed pathogenic mechanism of missense and splicing mutations*. The majority of missense mutations inside and outside exon 10 reduce tau binding to microtubules and directly accelerate tau aggregation. Mutations in exon 10 only affect 4R tau while those outside exon 10 affect all isoforms. Splicing mutations (except ΔK280) increase the level of 4R tau, which results in neurodegeneration possibly through an increase in unbound 4R tau or through a direct acceleration in aggregation. Microtubule binding domains are in grey, exons 9–12 are indicated by black boxes, missense mutations are indicated by X.

shown that the majority of missense mutations cause a partial loss of tau–microtubule binding.

A second potential pathogenic effect of the missense mutations may be to alter the tendency of tau to form aggregates. Studies in which recombinant wild-type and mutant tau is incubated in the presence of either heparin or archidonic acid have indicated that at least some of the FTDP-17 missense mutations are able to accelerate tau filament formation. Data from two parallel studies showed that the P301L and P301S mutations were associated with the greatest increase in filament formation compared to wild-type tau (Goedert et al., 1999; Nacharaju et al., 1999). It might well be that some of the FTDP-17 missense mutations have a double pathogenic mechanism that initially involves reduction of microtubule binding with an increased tendency of the unbound tau to polymerise into insoluble filaments (Fig. 3). A recent report has further suggested that some of the missense mutations (R406W, G389R) decrease tau degradation by calpain resulting in an increased level of tau available for aggregation (Yen et al., 1999).

3.2. Missense and 5′ splice site mutations that modify alternative splicing of tau exon 10

Mutations that disrupt tau exon 10 alternative splicing have been found both in intron 10 (at positions +3, +13, +14 and +16 relative to the splice site) and exon 10 (N279K, ΔK280, L284L, S305N) (Hutton, 1999). The effects of 5′ splice site mutations on exon 10

alternative splicing have been studied by RT-PCR analysis of FTDP-17 brains and exon trapping (Hutton et al., 1998). These studies demonstrated an increase in exon 10 + tau mRNA thus increased splicing inclusion of exon 10. Analysis of soluble tau from the brains of splice site mutation cases also showed an increase in the ratio of 4R tau to 3R tau corresponding to the altered RT-PCR results (Spillantini et al., 1998b). Examination of the intronic sequence downstream of exon 10 and the secondary structure of in vitro transcribed RNA demonstrated that a stable stem-loop can form at this position, which is disrupted by the intronic mutations (Varini et al., 1999). In addition, these studies showed that exon-trapping analysis using artificial exon 10 constructs with stem-loops of varying stability produced results consistent with the regulation of alternative splicing by the predicted stem-loop (Grover et al., 1999). In contrast, splicing assays in which the stem-loop mutations are rescued by altering the complementary residue on the opposite side of the stem-loop so that base pairing is restored have given variable results (D'Souza et al., 1999; Grover et al., 1999). This has led to controversy over the significance of the stem-loop. An alternative hypothesis is that the intronic mutations disrupt a novel type of negative regulatory element that acts as a recognition sequence for a *trans*-acting splice factor. Although the splicing mechanism is not resolved yet, it is clear that mutations in the intron close to the 5′ splice site of exon 10 increase the proportion of exon 10 + mRNA and thus 4R tau.

Four mutations within exon 10 affect alternative splicing of exon 10 (N279K, ΔK280, L284L and S305N) (Fig. 2c) (D'Souza et al., 1999). The N279K mutation strengthens a poly purine element, while the L284L mutation eliminates a potential negative *cis*-acting element, both resulting in an increase in exon 10+ RNA (Hong et al., 1998; D'Souza et al., 1999). The S305N mutation alters the −2 residue relative to the 5′ splice site and is predicted to directly increase U1 snRNP binding to the 5′ splice site, thereby increasing the level of 4R tau as well as disrupting the stem-loop structure (D'Souza et al., 1999). ΔK280 is the only mutation that decreases exon 10 inclusion and thus is predicted to result in the decrease of the level of 4R tau. The ΔK280 mutation is interesting because in addition to eliminating exon 10 inclusion in vitro, it also disrupts tau–microtubule binding (D'Souza et al., 1999; Rizzu et al., 1999).

In summary, the identification of mutations that disrupt alternative splicing of exon 10 has revealed three different *cis*-acting splice regulatory elements: a poly-purine tract splice enhancer in exon 10, a negative element (possibly UUAG) adjacent to the poly-purine tract, and a negative element immediately downstream of the 5′ splice site, which is probably the proposed stem-loop structure. Preliminary data also suggest that further intronic and exonic *cis*-elements are also present (author's unpublished results). This suggests that regulation of exon 10 alternative splicing is a complex process involving interaction between multiple *cis*- and *trans*-acting factors. This likely explains why there are different ratios of 4R to 3R tau in different brain regions and why during foetal development only 3R tau is produced in the brain, with 4R isoforms appearing some time after birth (Goedert et al., 1989).

4. Tau polymorphisms in PSP and CBD

In addition to the identification of highly penetrant tau mutations in FTDP-17 families,

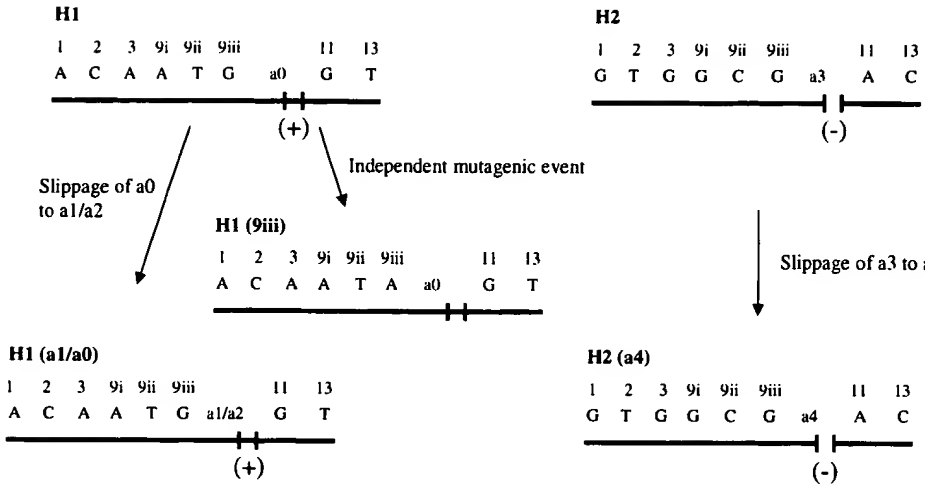

Fig. 4. *Human tau haplotypes and association with PSP and CBD.* Schematic representation of Human tau gene haplotypes. Ancestral haplotypes H1 and H2 are defined by a series of polymorphisms throughout the tau gene (>100 kb) that are in complete linkage disequilibrium with each other. H1 and H2 have been modified by subsequent mutational events (examples are shown) however no recombination is observed between H1 and H2 haplotypes (H1–H1 and H2–H2 recombination may occur). +/− symbols indicate a deletion/insertion polymorphism upstream of exon 10. a0–a4 alleles of the dinucleotide polymorphism between exons 9 and 10. Inheritance of the H1/H1 genotype is a significant genetic risk factor for the development of PSP and CBD, however the critical polymorphism(s) that influence pathogenesis have not yet been identified.

variability in the tau gene has also been shown to be a risk factor for another tauopathy, PSP (Conrad et al., 1997; Baker et al., 1999). PSP is a rare parkinsonian movement disorders that is associated with early postural instability and supranuclear vertical gaze palsy (Litvan and Hutton, 1998). The brains of patients display neurofibrillary tangles that are primarily localised to the subcortical region. The tangles that are observed in PSP contain predominantly four-repeat tau-isoforms consisting of straight filaments (Spillantini et al., 1998a).

An initial study of tau variability in PSP demonstrated that one allele of a dinucleotide polymorphism (A0), between exon 9 and exon 10, was associated with the development of PSP with presence of an excess of A0/A0 homozygotes within PSP cases (Conrad et al., 1997). Subsequent studies have further shown that this polymorphism is inherited as part of two extended haplotypes (H1 and H2) that cover the entire tau gene (>100 kb) (Baker et al., 1999). No recombination has been observed between the H1 and H2 haplotypes (Fig. 4). Inheritance of two copies of the common haplotype (H1) in the tau gene is strongly associated with the development of PSP (87.5% in PSP cases, 62.8% in controls; $\chi^2 = 13.85$, $P < 0.001$) (Baker et al., 1999). Recent data has provided evidence that the same tau haplotype association is a risk factor for developing CBD (author's unpublished results). It is currently unclear, however, which specific polymorphism or combination of polymorphisms within the tau H1 haplotype produces the increased risk for the development of PSP and CBD. One possibility is that exon 10 splicing is altered in PSP and CBD

consistent with the selective deposition of 4R tau; however, no polymorphisms have yet been identified that are likely to modify alternative splicing. These data clearly provide further genetic evidence for a central role for tau in the pathogenesis of PSP and CBD.

5. Mice expressing wild-type tau and the P301L FTDP-17 mutation

Only tau isoforms containing all four microtubule-binding domains are produced in mouse brains as opposed to the approximately 1:1 ratio of 4R to 3R in adult human brain. Several transgenic mouse models have been produced, which express either the shortest (WT3R0N) or the longest isoform (WT4R2N) of human wild-type tau (Götz et al., 1995; Brion et al., 1999; Ishihara et al., 1999; Spittaels et al., 1999; Probst et al., 2000). The low level of expression of either the wild-type 3R0N or 4R2N resulted in the somadendritic localisation of tau as well as evidence of tau hyperphorphorylation (Götz et al., 1995; Brion et al., 1999). Mice expressing the human wild-type 4R2N at higher levels developed axonal degeneration and motor dysfunction (Spittaels et al., 1999; Probst et al., 2000). Transgenic expression of wild-type 3R0N at high levels in mice caused accumulation of insoluble, hyperphosphorylated tau, argyrophilic tau positive inclusions in the brain and spinal cord, and some of motor dysfunction (Ishihara et al., 1999). Although the tau inclusions from these mice were silver positive, they lacked the fibrillary nature of classic tau tangles since they were Thioflavin S negative. Despite the progress in developing a mouse model with tau dysfunction, neurofibrillary tangles have previously been absent in the reported tau animal models. In contrast, a new transgenic mouse model expressing human tau with the P301L mutation develops neurofibrillary tangles, neuronal loss and severe motor dysfunction (author's unpublished results). The neurofibrillary tangles from these animals were argyrophilic, Thioflavin S and Congo Red positive (Fig. 5). Electron microscopy of the tau inclusions showed the presence of both straight and twisted ribbon filaments similar to those found in other tauopathies. The neurofibrillary pathology was also associated with 50% cell loss in the spinal cord. This mouse model mimics many key features of FTDP-17 and related tauopathies, making it a good model to study neurodegeneration related to tau accumulation.

6. Summary and conclusions

Multiple missense and splice site mutations in tau are pathogenic for a group of tauopathies known collectively as FTDP-17. To date, 16 tau mutations in more than 50 families have been identified making it a major cause of autosomal dominant neurodegenerative dementia. The identification of tau mutations has provided clear evidence that tau dysfunction can result in neurodegeneration. Variability in the tau gene has also been shown to be a risk factor for the development of PSP and CBD. This suggests that tau plays a central role in the pathogenesis of most, if not all, the tauopathies.

The identified FTDP-17 missense and splice site mutations have multiple effects on the biology of tau. The exon 10 splicing mutations (N279K, L284L, and exon 10 5′ splice site -2 to $+16$) increase the proportion of exon 10 + mRNA and thus the ratio of 4R to 3R isoforms. Increasing the ratio of 4R to 3R tau by as little as two-fold results in FTDP-17;

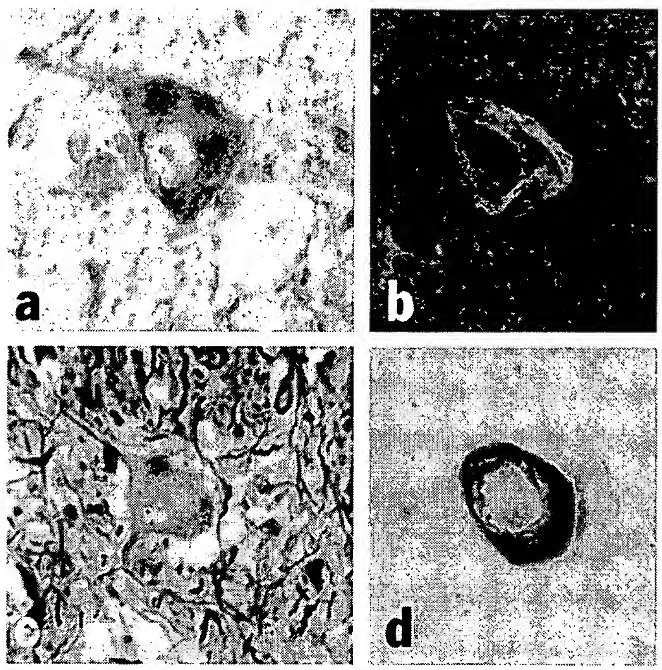

Fig. 5. *Neurofibrillary tangles in transgenic tau P301L mice.* Neurofibrillary tangles are shown from the spinal cord of P301L transgenic mice with immunostaining (CP13) (a) and thioflavin-S fibrillar straining of NFT (b). Some NFT were weakly stained with Bielschowsky's silver stain (c). More were stained with Gallyas silver iodide (d).

however, the mechanism by which this shift in ratio leads to neurodegeneration remains unclear. One possibility is that saturation of specific 4R tau binding sites on microtubules causes an increase in unbound tau available for aggregation into filaments (Fig. 3). It is also possible that an increase in 4R Tau directly accelerates at least part of the aggregation process in vivo (Fig. 3) although it is not clear how this hypothesis fits with current nucleated assembly models of tau aggregation (Friedhoff et al., 1998). In contrast, the ΔK280 mutation reduces the proportion of exon 10 + transcripts in exon trapping assays. Additionally, this mutation also produces a dramatic reduction in tau–microtubule binding. However, the pathogenic mechanism of ΔK280 remains unclear since pathological findings are not available. The majority of missense mutations disrupt the interaction between Tau and microtubules. The disruption of this interaction is expected to increase the level of unbound tau in neurons that is available for aggregation. In addition, at least some missense mutations also appear to directly increase the tendency of tau to self-interact and form filaments. The overall effect of the majority of FTDP-17 missense mutations is thus predicted to be an increase in the rate of tau aggregation and eventually the formation of the insoluble tau inclusions that are a feature of FTDP-17.

Data on the mechanism of tau mutations published so far is derived from in vitro studies. The newly developed transgenic animal model expressing tau with the P301L

mutation is a breakthrough in the tau field, providing an experimental animal model for cell loss and filamentous tau deposits in vivo (Grover et al., 1999).

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